REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. Status Of Claims And Formal Matters

Claims 1-27 were under consideration in this application. Claims 4, 6, 7, 10-14, 16, 19-22, 24 and 25 have been canceled and claims 28-46 have been added. Support for the claim amendments is found throughout the specification as originally filed. No new matter has been added by this amendment.

The Examiner is thanked for withdrawing the rejection of claims 1-3, 8, 9, 15, 17 and 18 under 35 U.S.C. § 112, second paragraph. The Examiner is also thanked for withdrawing the rejections under 35 U.S.C. § 102. The Examiner is further thanked for indicating that claim 22 is free of the prior art and in condition for allowance.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Claim Objections are Overcome

Claim 4 was objected to as allegedly being a substantial duplicate of claim 14. Claims 4 and 14 have been canceled, thereby rendering the objection moot.

Claim 24 was objected to as allegedly being a substantial duplicate of claim 25. Claims 24 and 25 have been canceled, thereby rendering the objection moot.

Claim 20 was objected to as being dependent upon a rejected base claim. Claim 20 has been canceled, thereby rendering the objection moot.

It is believed that the objections to the claims have been overcome. Reconsideration and withdrawal are respectfully requested.

3. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

Claims 4, 6, 7, 10, 11, 14, 16, 21, 24 and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide enablement for a method for specifically delivering to

tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium selected from the group consisting of a genus *Bifidobacterium*. The Office Action admits that the specification is enabling for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein.

Claims 4, 6, 7, 10-14, 16, 19-22, 24 and 25 have been cancelled, thereby obviating the rejection.

Applicants presently claim transformed bacterium belonging to the genus *Bifidobacterium* to a bacterium belonging to the genus *Bifidobacterium*, selected from the group consisting of B*ifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium pseudolongum, Bifidobacterium thermophilium, Bifidobacterium breve,* and *Bifidobacterium infantis*.

The above transformed bacterium belonging to the genus *Bifidobacterium* relates to a bacterium belonging to the genus *Bifidobacterium* comprising a promoter and terminator involved in expressing a gene encoding a histone-like DNA-binding protein of a bacterium belonging to the genus *Bifidobacterium*, and transformed with an expression vector in which an DNA encoding a protein having an antitumor activity (a), or a protein having an activity to converting a precursor of an antitumor substance (P) into an antitumor substance, is integrated to the downstream of the promoter, selected from the group consisting of *Bifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium pseudolongum, Bifidobacterium thermophilium, Bifidobacterium breve,* and *Bifidobacterium infantis*. As it is obvious to a person skilled in the art that the promoter and terminator involved in expressing a gene encoding a histone-like DNA-binding protein of a bacterium belonging to the genus *Bifidobacterium* functions in the above bacterium belonging to the genus *Bifidobacterium,* the enablement requirement is fulfilled.

The Office Action recites: "the state of the art for transforming bacterium from the genus Bacterium is highly unpredictable" by reciting Argini *et al.* (IDS, Microbiology, Vol. 142, pp. 109-114) as follows. "Although electropolation technique has proven to be widely applicable to

genetically transform bacterial strains, all Bifidobacterium so far examined have proved refractory to efficient and reproducible transformation (page 109)."

However, there is the statement following this statement: "In this paper we describe the development of a system for efficient and reproducible genetic transformation of strains of the genus *Bifidobacterium*. The system is based on preincubation buffer prior to electroporation, and on the use of plasmid vectors with a replicon from *Actinomycetaceae*." (p.109, right column, lines 21 to 27).

Thus, the main object of Argnani *et al.* is "A convenient and reproducible method to genetically transform bacteria of the genus *Bifidobacterium*".

Further, the Office Action alleges that the enablement requirement is not fulfilled for bacteria other than *Bifidobacterium longum*, by referring to the following statement of Yazawa *et al.* (Breast Cancer Research and Treatment, Vol. 66, pp. 165-170, 2001): "*Bifidobacterium* is non-pathogenic bacteria found in the intestine of human and some other mammalian animals. These organisms are believed to have health-promoting properties for their host, including increase of the immune response, inhibition of carcinogenesis, and protection of the host against viral infections. However, despite increasing attention to this bacterium in many fields, little is known about its genetic property (page 165)."

However, Yazawa *et al.* states in p. 169, right column, lines 19 to 29, as a conclusion, that a bacterium belonging to the genus *Bifidobacterium* can be used, and that *Bifidobacterium* is useful for the treatment of a solid tumor, and the statement is not limited to *Bifidobacterium longum*.

These recitations are also supported by the reference of Li *et al.* (Cancer Gene Therapy, 2003: 10: 105-111) which was published after the present application has been filed. The Examiner is respectfully requested to consider and make of record the article by Li *et al.*, which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

Li et al. relates to using *Bifidobacterium infantis* which is a bacterium belonging to the genus *Bifidobacterium*, other than *Bifidobacterium longum*. It is clear that Li et al. has referred to Yazawa *et al.*, and that Li *et al.* practiced the present invention according to the knowledge of Yazawa *et al.*

These recitations are also supported by the reference of Yi *et al.* (Acta Pharmacologica Sinica, 2005: 26: 629-634) which was published after the present application has been filed. The Examiner is respectfully requested to consider and make of record the article by Yi *et al.*, which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449. Yi et al. relates to using *Bifidobacterium infantis* in a targeted gene therapy system.

Accordingly, the disclosure is enabling for other bacterium in the *Bifidobacterium* family, in addition to *Bifidobacterium longum*.

It is believed that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome. Reconsideration and withdrawal are respectfully requested.

4. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 4, 6, 7, 10-14, 24 and 25 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner alleges that claims 1-4, 6-15 and 24-25 are incomplete for omitting essential steps, such omission amounting to a gap between the steps.

Claims 4, 6, 7, 10-14, 16, 19-22, 24 and 25 have been cancelled, thereby obviating the rejection.

It is believed that the rejections under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal are requested.

5. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 4, 6, 7, 10, 12, 14, 16, 19, 21, 24 and 25 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa *et al.* (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) (hereinafter "Yazawa 2") taken with Brown (AC). These rejections are respectfully traversed and are moot in light of the amendments to the claims submitted herein. The citeds reference do not make the instant invention obvious.

Claims 4, 6, 7, 10-14, 16, 19-22, 24 and 25 have been cancelled, thereby obviating the rejection.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re*

Fritch, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention.

The present invention relates to a gene delivery vector which proliferates under anaerobic conditions, transformed so that it can produce a protein having an antitumor activity (a) or a protein having an activity of converting a precursor of an antitumor substance (P) into an antitumor substance, having a promoter or terminator involved in expressing a gene encoding a histone-like DNA-binding protein of the genus *Bifidobacterium*, and transformed with an expression vector in which an DNA encoding the protein having an antitumor activity (a) or a protein having an activity of converting a precursor of an antitumor substance (P) into an antitumor substance; selected from the group consisting of *Bifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium pseudolongum, Bifidobacterium thermophilium, Bifidobacterium breve,* and *Bifidobacterium infantis*.

Yazawa 2 does not teach or suggest a gene delivery vector having a promoter and terminator involved in expressing a gene encoding a histone-like DNA-binding protein of a bacterium belonging to the genus *Bifidobacterium*, and transformed so that it can produce a protein having an antitumor activity or a protein having an activity of converting a precursor of an antitumor substance into an antitumor substance, in the downstream of the promoter.

On the other hand, Brown relates to a method for delivering to a tumor tissue, a DNA having an activity of transforming a precursor of an antitumor substance into the corresponding antitumor substance, a method wherein the protein having an activity of converting a precursor of an antitumor substance into the antitumor substance is nitroreductase, the precursor of antitumor substance is CB1954, and the anaerobic bacterium of the gene delivery vector is *Clostridium acetobutylicum*. However, the bacterium belonging to the genus *Clostridium*, to which *Clostridium acetobutylicum* belongs, comprises many pathogenic bacteria including *Clostridium tetani* of tetanus bacilli, *Clostridium botulinum* or *Clostridium perfringens* which are

pathogenic bacteria causing food poisoning, *Clostridium difficile* inducing diarrhea, and differ completely with non-pathogenic bacteria which are present in human intestine, such as the bacteria belonging to the genus *Bifidobacterium* of the present invention, and naturally, the characteristics and the function of the carrying plasmid differ as well.

The method of gene delivery of Brown is a method using sporulation specific to the bacterium belonging to the genus *Clostridium* (see for example, Example 2D), and differs completely with the method using nurse cells itself, such as the bacteria of the present invention.

As the Office Action alleges that the specification is not enabled for bacteria belonging to the genus *Bifidobacterium*, it is unreasonable to combine Brown, wherein the promoter, terminator and further the transforming method is different, with Yazawa 2, by using a bacterium belonging to the genus *Clostridium*, and sporulation, which is completely different with the bacterium belonging to the genus *Bifidobacterium*.

As stated above, the gene delivery vector of Brown differ from the point of view of the genus of bacterium with that of the present invention, thus, the characteristics and the function differ completely as well. As the transforming method as well as the characteristics and function of the vectors differ completely, the present invention is not obvious from Brown or Yazawa 2 Moreover, a person skilled in the art would not have been motivated to combine Brown with the *Bifidobacterium* of Yazawa 2.

In view of the present claim amendments, there is no motivation to combine Yazawa 2 and Brown. Even if the references were combined, the combination of Yazawa 2 and Brown would not teach or suggest the presently claimed invention.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

No fee is believed to be due. The Commissioner is hereby authorized to charge any additional fee which may be required for this paper, or credit any overpayment to Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: Deborah L. Lu

Thomas J. Kowalski
Reg. No. 32,147
Deborah L. Lu
Reg. No. 50,940
Telephone: (212) 588-0800
Facsimile: (212) 588-0500